

## **Cameron Benign and Malignant Brain Tumor Review, 2008 – 2009**

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### **Executive Summary**

Few families are untouched by cancer. Cases that are close together in time or space may have a shared cause or may be a coincidental occurrence. The Missouri Department of Health and Senior Services (DHSS) Cancer Inquiry (CI) process managed within the Division of Community and Public Health was established to determine if a community of interest has a higher cancer burden than expected based on state rates of disease or death.

While education is provided in response to each CI in Missouri, not all states offer these services due to the low yield in identifying clusters or, if found, the rarity in identifying a reason why the cluster exists. These efforts are often hampered by having too few cases to have a sufficient sample size from which to make statistical inferences. To address this, some states may limit conducting cluster investigations to specific settings (e.g. workplace-related clusters) where the exposure levels may be higher and where improved documentation of who was and was not exposed exists.

In Missouri, a multi-discipline and multi-agency approach is used to respond to resident inquiries about the possibility of a cancer cluster. DHSS and the Missouri Department of Natural Resources (DNR) partner together with the Missouri Cancer Registry (MCR) at the University of Missouri Columbia, to use the specialties of their disciplines and surveillance/testing systems to respond to cancer inquiries.

In 2004, benign brain tumors were added to the list of diagnoses collected in a nationally standardized way by the MCR, allowing the inquiry process to expand and include this category of benign tumor. For simplicity, this report will refer to CI as the process of evaluating rates of tumor-related disease, benign or malignant.

This cancer inquiry began on April 11, 2008, when a community member contacted DHSS to express concern over the number of benign brain tumors occurring in the Cameron area; shortly thereafter the inquiry was expanded to include malignant brain tumors. Reportable benign and malignant brain tumors are the primary focus of the statistical analysis in this report. Numerator data (i.e., the cases) come from the MCR, death certificates, patient information forms that meet the criteria of the inquiry case definition, and a special Rapid Case Ascertainment (RCA) process completed specifically for this inquiry through which the MCR requested that hospital-based tumor registries and other reporting entities report to the registry ahead of schedule any tumors that meet the case definition of this review. Cancer registries from as far away as Texas responded to this request to assist Missouri in identifying as many potential cases of benign and malignant brain tumors as possible from the Cameron area. As part of quality improvement processes, MCR was audited in 2008 by CDC's contractor, Macro International. The audit was done on diagnoses reported in 2005. The completeness rate was 96.7%. MCR was specifically mentioned as having no missed benign brain tumor cases. The Missouri Cancer Registry has also been acknowledged by the North American Association of Central Cancer Registries (NACCR) as being of the highest standard ('gold-certified') level designation in both 2008 and 2009.

Two previous CIs were requested in 1996 and 2002 in this geographic area, though neither found evidence of increased cancers of concern. Environmental risk factors suggested by community members at that time were agricultural pesticides and contaminated reservoir water, though due to the

fact that a cluster was never statistically identified, progress to the CI protocol step of conducting environmental sampling was not completed as part of those CIs.

As part of the current cancer inquiry, the University of Missouri-Columbia was contracted to complete a geospatial analysis of reported disease statewide. The SatScan analysis was completed in August 2009 on the most recent dataset submitted to the National Program of Cancer Registries (data submitted to CDC in December 2008 covering validated case reports through 2006). These analyses did not identify statistically significant clusters of benign or malignant brain tumors in Cameron or the four counties (DeKalb, Daviess, Clinton, and Caldwell).

**Findings:**

Due to very active public involvement in this inquiry, ninety-nine patient listing forms reporting a variety of diseases among individuals in multiple states over a 40-year time frame were returned to the DHSS. All were cross-checked with the Missouri Cancer Registry. When possible, follow-up telephone calls to gather missing information were made to hospitals, physician's offices, and some patients and families. The Missouri Cancer Registry requested rapid case ascertainment (RCA) from all hospitals in Missouri; through case-sharing agreements with central registries in other states, the same request was made to referral hospitals frequently used by Missouri residents. This request asked for immediate reporting of all cases of brain and other reportable central nervous system malignant and benign tumors diagnosed among residents from any of the four counties included in the Cameron zip code.

Data for this report include Missouri Cancer Registry data, Rapid Case Ascertainment early diagnoses, and information from patient information forms (PIF) that met the criteria of the case definition. Twenty-nine benign (2004-2008) or 49 malignant (1996-2008) brain or other central nervous system tumors were confirmed in the four-county area and are included in this analysis. Preliminary review of 2009 cases has identified 3 additional malignant or benign brain tumors in the area.

The analyses compared the observed and expected number of cases meeting the case definition. The expected number of cases is based on what would be expected if the Missouri rate of brain tumors was what was experienced locally, too. Few cases occurred within the zip code specific to Cameron. Analysis was completed by county and the 4-county area which the Cameron zip code touches. Because there were no statistical differences between smaller and larger units of geography under comparison, the 4-county area is used so the confidence intervals can be as narrow as possible and the power to detect any differences between the community and the state is maximized.

County-specific data on self-reported behavioral risk factors and items such as access to health care or the percent of the population having health insurance is available from the 2007 Missouri County Level Study at <http://www.dhss.mo.gov/CommunityDataProfiles/>. These county-specific fact sheets were distributed in the community in October 2008.

**Conclusion:**

The incidence of brain and other central nervous system tumors, malignant (January 1, 1996 – December 31, 2008) or benign (January 1, 2004 – December 31, 2008), in the four-county area around Cameron is similar to estimates from the Central Brain Tumor Registry of the United States (CBTRUS) and to comparisons with Missouri statewide data. There is no statistically significant increase in the mortality due to brain tumors (benign or malignant) in this community compared to the state of Missouri.

## **Discussion**

In a cancer inquiry to determine if there is an excess amount of brain tumors, epidemiologists look for four things: (1) elevated incidence of, or mortality due to, malignant or benign tumors of the brain or central nervous system (CNS), (2) concentration in one age group, (3) a disproportional distribution of cases over the brain cancer subtypes, and (4) an increase in other cancers that may be related to environmental sources. A case definition is ‘a set of standard criteria for deciding whether an individual should be classified as having the health condition of interest.’ Factors considered include clinical criteria (e.g., criteria for registration in the cancer registry) and a scope of the time (e.g., years of quality information, purported time between exposure and onset of disease for the health condition of interest), place (geographic area of interest), and person (e.g., workers at a specific plant or residents of a certain county, etc.). For this inquiry and in response to community input at the beginning of the inquiry and through community meetings, the **case definition** is:

For primary malignant brain and CNS tumors diagnosed between January 1, 1996 through December 31, 2009

- Residence in Caldwell, Clinton, Daviess, or Dekalb County (the counties with part of the Cameron zip code included in them) at the time of physician diagnosis of a malignant brain or central nervous system tumor (meeting the National Program of Cancer Registries classification for such tumors (ICD-O-3 coding)).
- Data from the Missouri Cancer Registry (MCR) used for 1996-2007 has now been externally verified through the Centers for Disease Control and Prevention (CDC) as 95% or more complete, whereas case data from 2008 are projected as 90% complete. Data through 2009 were obtained only through early reports to the MCR and by self-reports from patients or those who know them via the Patient Information Forms, thus the 2008-2009 data have not gone through the same rigorous validation process and should be considered provisional at best.
- Mortality data arise from death certificate submission to the DHSS Bureau of Vital Records and cover the same four-county area for the time period of 1999-2008 (ICD 10 coding).
- All data included were received by February 24, 2010.

For benign brain and CNS tumors diagnosed between January 1, 2004 through December 31, 2009.

- Residence in Caldwell, Clinton, Daviess, or Dekalb County (the counties with part of the Cameron zip code included in them) at the time of physician diagnosis of a benign brain or central nervous system tumor (meeting the National Program of Cancer Registries classification for such tumors (ICD-O-3 coding)).
- Data from the Missouri Cancer Registry (MCR) used for 2004-2007 has been externally verified through the CDC as 95% or more complete, whereas case data from 2008 are projected as 90% complete. Data from 2009 were obtained only through early reports to the MCR and by self-reports from patients or those who know them via the Patient Information Forms, thus the 2008-2009 data have not gone through the same rigorous validation process and should be considered provisional at best.
- Mortality data arise from death certificate submission to the DHSS Bureau of Vital Records and cover the same four-county area for the time period of 1999-2008 (ICD 10 coding).
- All data included were received by February 24, 2010.

## INCIDENCE

There were 78 total people meeting the case definition for inclusion in this inquiry; 29 were diagnosed from the 4-county area with primary benign or unclassified tumors between 2004 and 2008 (not significantly different from the 33.5 cases expected based on the state rate) and 49 were diagnosed with primary malignant tumors between 1996 and 2008 (not significantly different from the 53.7 cases expected based on the state rate). Addition of 2009 data received thus far (for which state comparison data are not yet available) adds a total of three cases of either malignant or benign for the 4 county region.

One way to determine if one geographic area has a higher incidence rate of disease (i.e. new cases per population for a given period of time) than another area is through a calculation called a standardized incidence ratio (SIR) and its' 95% confidence interval (meaning you are 95% certain that the number falls within this range). An SIR of 1.0 means the two populations' incidence rates are the same. An  $SIR < 1.0$  means the risk is lower (to some degree) and an  $SIR > 1.0$  means the risk is higher (to some degree) than the reference population (in this case, the state of Missouri). These incidence rates are adjusted for patient race, gender, and age. Analysis was completed by age-group within the 4-county area. Because there were no statistical differences between smaller and larger units of geography under comparison, the 4-county area is used so the confidence intervals can be as narrow as possible and the power to detect any differences between the community and the state is maximized. Because multiple comparisons are made of the dataset, a p value of 0.01 is selected for detecting a significant difference between rates.

The standardized incidence ratio (SIR) for benign brain tumors in the area of concern was 0.87, with a 95% confidence interval of 0.58 to 1.24. The number of benign brain tumors was 29, which is not significantly different from the expected number of cases of 33.5, calculated based on the state rate. In terms of malignant brain tumors, the SIR was 0.91, with the 95% confidence interval being 0.68 to 1.2. There were 49 cases compared to 53.7 expected based on state rates, for a p value of 0.29. Age-specific incidence rates for benign (Table 1) and malignant (Table 2) brain tumors follow.

Table 1. Observed and expected number of cases of benign/borderline brain and other CNS tumors in the four county area 2004-2008

Age	Observed	Expected*	P value	Poisson Test of Significance ( $P < 0.01$ )	SIR**	Lower 95% CI***	Upper 95% CI
0 - 19	4	1.0	0.020	NS <sup>±</sup>	3.906	1.064 <sup>f</sup>	10.002
20- 34	0	2.4	0.087	NS	0.000	0.000	1.229
35 - 54	10	9.9	0.525	NS	1.014	0.486	1.864
55 - 74	10	12.9	0.263	NS	0.777	0.373	1.429
75+	5	7.3	0.260	NS	0.682	0.221	1.592
All Ages	29	33.5	0.248	NS	0.865	0.579	1.242

\* Expected based on age-, race-, and gender-specific state rates.

\*\* SIR: Standardized Incidence Ratio

\*\*\*CI: Confidence Interval of the ratio

<sup>±</sup> NS: Not Significant

<sup>f</sup> Significant at p=0.05 level

Even though the confidence interval of the SIR for age group 0-19 indicates an elevated rate, the observed is not significantly different from the expected for this age group. In addition, the four benign tumor cases are in four different counties, so no cluster is identified.

Table 2. Observed and expected number of cases of malignant brain and other CNS tumors in the four county area 1996-2008

Age	Observed	Expected*	P value	Poisson Test of Significance ( $P<0.01$ )	SIR**	Lower 95% CI***	Upper 95% CI
0 - 19	3	5.8	0.168	NS <sup>‡</sup>	0.515	0.106	1.506
20 - 34	4	4.0	0.625	NS	0.996	0.271	2.549
35 - 54	15	12.3	0.259	NS	1.216	0.681	2.006
55 - 74	18	20.3	0.353	NS	0.885	0.524	1.398
75+	9	11.2	0.317	NS	0.802	0.367	1.522
All Ages	49	53.7	0.287	NS	0.912	0.675	1.205

\* Expected based on age-, race-, and gender-specific state rates.

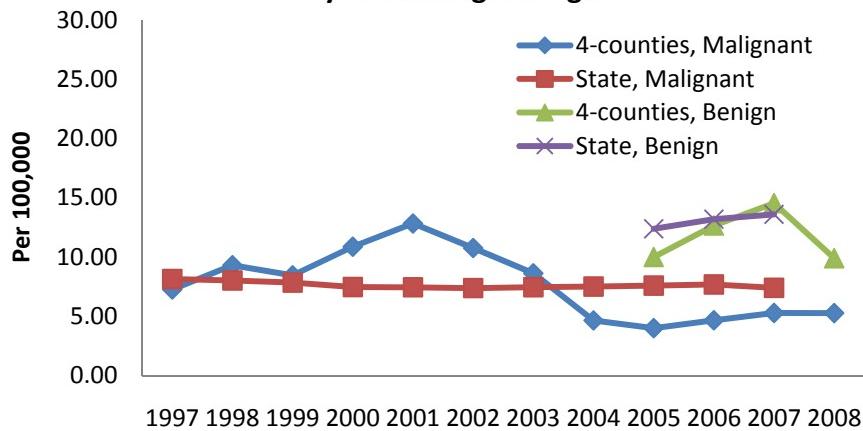
\*\* SIR: Standardized incidence ratio

\*\*\*CI: Confidence Interval of the ratio

<sup>‡</sup> NS: Not Significant

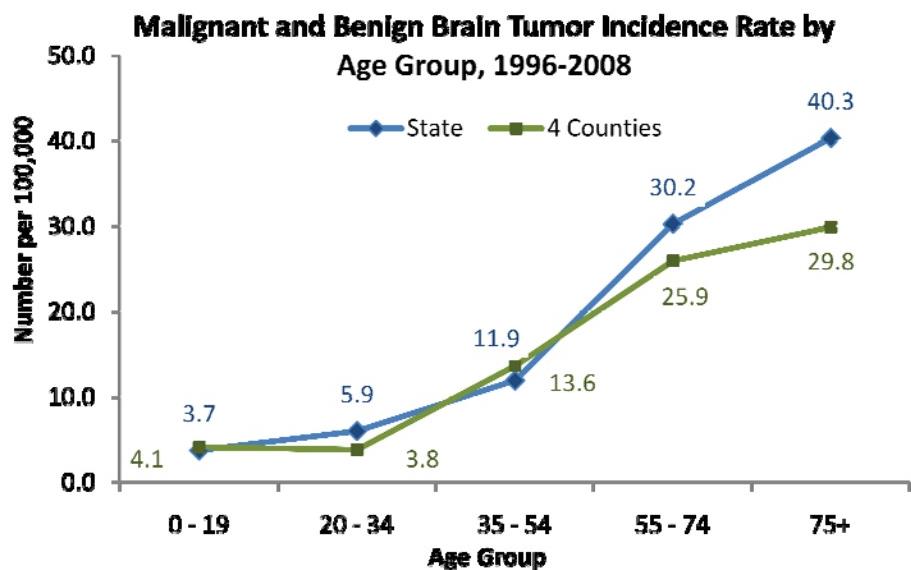
Another way to look at incidence is by time. A smoothing technique used on data from small populations is to take a 3-year moving average of incidence rates.

### Malignant and Benign Brain Tumor Incidence Rates 3-year moving averages



As a comparison with other states, the Central Brain Tumor Registry of the United States (CBTRUS) estimated incidence of primary brain tumors of population-based registry data from 18 states is 18.28/100,000 (18.16-18.40) for 2002-2006.

The age-specific incidence rate of primary malignant and benign tumors combined in the area of concern compared to Missouri is shown next. The age-specific incidence rates between the four county area and the State are not statistically different from one another.



Geospatial analysis of benign or malignant brain tumor diagnosis by place of residence in Missouri at the time of diagnosis did not detect any significant clusters of increased incidence in Cameron or any of the four counties the Cameron zip code touches.

To help address how common malignant or benign brain tumors are in the Cameron area compared to statewide in Missouri, the Missouri Cancer Registry data were reviewed to determine the percent of diagnosis-specific events reported to the registry and to rank the ten most common events reported. Because benign brain tumors were included and compared to statewide data, only data from the years 2004-2008 were included.

#### Cameron 4-County Area

1. Lung and Bronchus (17.3%)
2. Prostate (13.6%)
3. Colon and Rectum (12.6%)
4. Female Breast (11.6%)
5. Urinary Bladder (4.4%)
6. Kidney and Renal Pelvis (4.4%)
7. Non-Hodgkin Lymphoma (4.0%)
8. Corpus and Uterus, NOS (3.4%)
- 9. Benign and malignant brain (3.1%)**
10. Melanoma of the Skin (2.9%)

#### Missouri

1. Lung and Bronchus (17.1%)
2. Female Breast (14.0%)
3. Prostate (12.8%)
4. Colon and Rectum (10.9%)
5. Urinary Bladder (4.3%)
- 6. Benign and malignant brain (4.2%)**
7. Non-Hodgkin Lymphoma (4.0%)
8. Kidney and Renal Pelvis (3.7%)
9. Melanoma of the Skin (3.6%)
10. Corpus and Uterus, NOS (2.9%)

## MORTALITY

Similar to comparing incidence in one geographic area to another, mortality comparisons are made through a standardized mortality ratio (SMR) calculation, with 95% confidence intervals and a p value calculated. Mortality due to benign and malignant brain tumors was not statistically different from what would be expected based on state rates of mortality.

Table 3, Observed and expected benign and malignant brain and other CNS tumor deaths in the four county area, 1999-2008

Age	Observed	Expected*	P value	Poisson Test of Significance (P<0.01)	SMR**	Lower 95% CI***	Upper 95% CI
0 - 19	2	1.1	0.298	NS±	1.830	0.222	6.610
20 - 34	3	1.2	0.116	NS	2.542	0.524	7.430
35 - 54	10	6.9	0.163	NS	1.442	0.692	2.652
55 - 74	14	14.9	0.476	NS	0.940	0.514	1.576
75+	13	11.5	0.367	NS	1.130	0.602	1.933
All Ages	42	35.6	0.161	NS	1.179	0.850	1.594

\* Expected based on age-, race-, and gender-specific state rates.

\*\* SMR: Standardized Mortality Ratio

\*\*\*CI: Confidence Interval of the ratio

± NS: Not Significant

## SUMMARY

- No clustering of brain tumor incidence or mortality is evident in Cameron compared to the state of Missouri.
- The Missouri statewide and Cameron area primary brain tumor incidence rates are lower than that published in the December 2009 report from the Central Brain Tumor Registry of the United States.
- Extensive environmental sampling has been done and has not resulted in identifying a biologically plausible environmental factor associated with brain tumor development in this community.
- Extending the follow-up period to include data submitted to the MCR to include data submitted to CDC in December 2009 identified 8 more cases of benign or malignant brain tumors and 3 additional deaths but the rates of disease or death remained similar to state rates.
- Future reports of the Central Brain Tumor Registry of the United States (CBTRUS) should include Missouri Cancer Registry (MCR) data.

CBTRUS (2009). 2009-2010 CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in Eighteen States in 2002-2006. Published by the Central Brain Tumor Registry of the United States, Hinsdale, IL. website: [www.cbtrus.org](http://www.cbtrus.org)